Remarks/Arguments

Claims 1, 2 and 8 are pending in this application and stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bottger et al., 1996 (Oncogene, 13:2141-2147), in view of McCann A H et al., 1995 (British J Cancer, 71(5):981-5), and further in view of Lee JM et al., 1995 (Cancer and Metastasis Review, 4(2): 1490161) "for reasons already of record in paper of 12/13/06." (Office Action, page 2)

In response to a previous similar rejection, Applicants advanced reasoned arguments and submitted a Declaration by Professor Karen Vousden explaining why the cited combination of references, when read in view of general knowledge in the art at the time the present invention was made, do not make obvious the claimed invention. The arguments and the declaratory evidence were, however, not found to be persuasive, since, according to the Examiner, McCann et al.

(i) teach that in most breast cancer patients, no mdm2 amplification or overexpression is detected;

(ii) show that "the expression of mdm2 in the commonly non-amplified mdm2 breast cancer is also associated with low expression of p53;"

(iii) teach that in familiar breast cancer patients lack of p53 mutation was reported, "thus p53 mutation may not contribute hereditary breast cancer." (Office Action, pages 4-5)

The Examiner notes that although, at the time the invention was made, in the specific breast cancer with no overexpression of Mdm2, the mechanism of p53 inhibition was unknown, in view of the cited teaching of McCann et al., and in view of the knowledge that mdm2 is a negative regulator of p53, "one would have been motivated to enhance the expression of p53, by disrupting the binding of mdm2 to p53." (Office Action ,sentence bridging pages 5-6) As further motivation to enhance the expression of p53 by disrupting the binding of mdm2 to p53, the Examiner refers to Bottger et al. as allegedly teaching that the peptide represents a clear route towards the design of small synthetic molecules that will

restore p53 function in human tumors, and lee et al. as allegedly teaching that loss of p53 function is correlated with resistance to chemotherapeutic agent. (Office Action, passage bridging pages 5 and 6).

With regard to the argument that the art taught that inhibition of mdm2 interaction with p53 could be deleterious to normal tissues, the Examiner notes that the claims are directed to an *in vitro* method and thus this argument is not relevant.

The Examiner notes that the "results from the instant invention are not a surprise" since (1) p53 is known to be negatively regulated by mdm2, and familiar breast cancers do not have p53 mutation; (2) low p53 is correlated with the expression of mdm2 in breast cancer, where most of breast cancer do not over-express mdm2; and (3) Bottger et al. teaches that a modified p53 peptide, which is "the same as the 12 amino acid peptide **MPRFMDYWEGLN** from the 19 amino acid, modified p53 sequence of the claimed invention, is effective displacing mdm2 from p53. (Office Action, page 8), and this has created a reasonable expectation that the peptide of the present invention would disrupt the binding of p53 and mdm2 in breast cancer cells in vitro. The Examiner adds that it would have been expected that the peptide does not inhibit the DNA specific binding property of p53, because "the peptide taught by the combined art would disrupt the binding of p53 to mdm2 by binding only at the specific p53 binding side for mdm2," which is different from the DNA binding site of p53. (Office Action, page 8)

Applicants continue to disagree with the Examiner's reading of the cited art, and submit a second declaration by Professor Karen Vousden to rebut the Examiner's assertions and the conclusions drawn from such assertions.

The Examiner clearly errs in interpreting McCann et al. to teach that MDM2 tumors are significantly associated with tumors having low levels of p53 staining.

In support of the conclusion that the expression of mdm2 in the commonly non-amplified mdm2 breast cancer is also associated with low expression of p53 (see above), the Examiner cites the Summary, lines 7-8 of McCann et al. as allegedly saying: *"at the protein level, MDM2 tumors were significantly associated with tumors having low levels of p53*

staining." As explained in paragraphs 4-8 of the Second Declaration of Professor Vousden ("the Second Vousden Declaration"), the cite is inaccurate, since in fact the paper refers to **MDM2+** tumors! This means that the authors restrict their comments only to the 7 (out of 97) MDM2+ (10-50% staining) tumors listed in Table II, and one cornerstone of the Examiner's arguments is removed. In fact, as Professor Vousden states in paragraph 8 of the Second Vousden Declaration, "*McCann et al. teach that tumours with high MDM2 expression are associated with low p53 and this is only 7% of the cancers*." (Emphasis added) As Professor Vousden notes, although some of the data, especially in Table III, might be conceivably interpreted to indicate that even tumors that express lower amounts of MDM2 are associated with low p53 levels, "*one might be reluctant to drawn conclusions from data that the authors have chosen not to highlight themselves.*" (Second Vousden Declaration, paragraph 9)

Even if one assumes that the results of McCann et al. indicate that MDM2 expression (either type 1 or type 2) is correlated with low p53, this is not sufficient basis for a conclusion that tumors that do not overexpress MDM2 are also associated with low p53 levels.

As explained in paragraph 10 of the Second Vousden declaration, McCann et al. did not include a normal tissue control in their experiment, and thus it is not clear what normal expression is. The fact that most of the tumors are negative for MDM2 staining does not mean that such tumors do not express MDM2, only that it is below the level of detection in that particular assay. As a result, this part of the data is hard to interpret, which might be a reason why the authors have chosen to base their conclusions on the tumors that clearly overexpress MDM2 (the type 2 staining ones).

McCann et al. teach that most breast cancers arise without evidence for amplification or overexpression of MDM2, and that such cancers are not associated with low levels of p53.

Absent comparative normal tissue data in the McCann et al. paper, it is unknown what MDM2 overexpression is. It is most likely that both type 2 and type 1 tumors are actually overexpressing MDM2, and the tumors with negative expression are those without overexpression. Using this interpretation of the McCann et al. data, even if type 1 tumors are taken into account (which the authors did not), it would still be clear that most breast cancers

arise without evidence of MDM2 overexpression or amplification, and these tumors are not associated with low levels of p53 (34/74 of them have type 3 and 3 p53 staining). See paragraph 13 of the Second Vousden Declaration. Thus, one of ordinary skill in the are would reasonably conclude, as Professor Vousden states in paragraph 14 of her Second Declaration, that in the 40 tumors without MDM2 staining and with low levels of p53 there must be another mechanism to inactivate p53, and that inhibiting the p53/MDM2 interaction would not necessarily work in such cases.

Accordingly, based on the results of McCann et al. in combination with the Bottger et al. study, and without the knowledge of the invention claimed in the present application, one of ordinary skill would reasonably conclude (as Professor Vousden does in paragraph 15 of her Second Declaration) that a treatment based on the 12 amino acid peptide would only be expected to be effective in 7% (or at most 22%) of breast cancer cells.

It is well established that expert declarations are entitled to serious consideration as long as they contain solid scientific arguments instead of mere conclusory statements. In assessing the probative value of an expert declaration, the Examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). In the present case, Professor Vousden is an unquestionable expert in the field with no personal interest in the outcome of the present matter, and therefore her declaration and the statements and analysis set forth in that declaration deserve serious consideration. It is submitted that in view of the explanation provided in that declaration, one of ordinary skill can only reach one conclusion, namely that the McCann eta l. paper, when taken alone or in combination with Bottger et al or Lee et al., does not make obvious the invention claimed in the present application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account 07-1700 (Attorney Docket No. 39749-0001 APC).

Respectfully submitted,

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